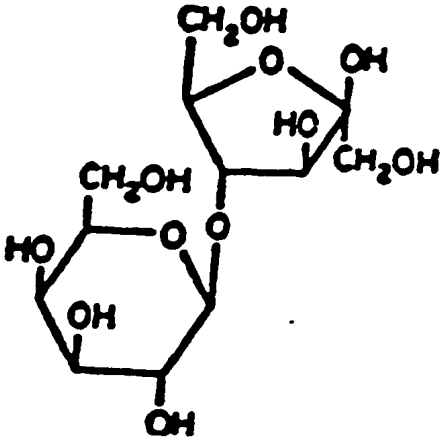
PRODUCT INFORMATION

DUPHALAC®

NAME OF THE MEDICINE

Lactulose

Chemical Structure



$C_{12}H_{22}O_{11}$ Lactulose mol wt 342.30

DESCRIPTION

Lactulose is 4-O-β-D-galactopyranosyl-D-fructose, a synthetic disaccharide of galactose combined with the furanose form of fructose, and produced by alkaline epimerisation of lactose. Lactulose is soluble in water, 76.4% w/w at 30°C.

Duphalac is a sweet, clear, colourless to slightly yellow liquid with a specific gravity of 1.33. Each 15 mL of Duphalac contains 10 g lactulose as the active ingredient, furthermore 1.5 g or less of galactose, 0.9 g or less of lactose, 0.7 g or less of epilactose, 0.3 g or less of tagatose, and 0.1 g or less of fructose.

Duphalac oral solution may also contain very small amounts of hydrogen peroxide and sodium hydroxide from the route of synthesis

PHARMACOLOGY

Therapeutic Category: Laxative

Experimental data on lactulose given orally to man indicate that lactulose is poorly absorbed from the gastrointestinal tract and no enzymes capable of hydrolysis of lactulose into its component monosaccharides are known to be present in human gastrointestinal tissue. Lactulose reaches the colon virtually unchanged. There it is metabolised by colonic bacteria to low molecular weight acids ie. lactic acid and other short chain carboxylic acids. Metabolism is complete at doses up to 25-50 g or 40-75 mL; at higher dosages, a proportion may be excreted unchanged.

Lactulose given orally to man results in only small amounts reaching the blood by absorption through the small intestine probably by a non-mediated diffusion mechanism. Otherwise small increases in blood sugar levels are probably attributable to the small amounts of galactose and lactose also present in Duphalac. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours. A small quantity of lactulose is probably hydrolysed in the colon into its constituent monosaccharides, galactose and fructose. The end result is a change in osmotic pressure and acidification of

the colonic contents resulting in an increase in stool water-content with resultant distention and softening of the stools, which in turn promotes increased peristalsis and bowel evacuation. In patients with chronic constipation, lactulose increases the number of bowel movements per day and the number of days when bowel movements occur.

Lactulose strengthens the growth of the health-promoting bacteria of the genus *Bifidobacterium* and may suppress potentially pathogenic bacteria like *Clostridium* and *Escherichia coli*. Consequently, it is often described as a prebiotic substance. Its effects on the balance of the intestinal flora may contribute to its action in hepatic encephalopathy (seeHepatic Encephalopathy , below).

Metabolism In Infants

Administration of lactulose to infants fed with cow's milk produces a predominance of *lactobacilli* in the stools, thus simulating the intestinal flora following maternal milk feeding. Lactulose also appears to increase the production of lysosome in infants receiving cow's milk.

Hepatic Encephalopathy

Hepatic Encephalopathy (HE) is a neuropsychiatric syndrome from a disorder of cerebral function, which can complicate all forms of liver disease. The major sites of cerebral involvement are the cortex extrapyramidal system and cerebellum. Clinical features include intellectual deterioration, disturbances of consciousness and neurological abnormalities.

It is generally accepted that HE involves exposure of the brain to nitrogenous substances arising from the gut from bacterial metabolism of protein, with ammonia being implicated most commonly, together with an alteration of the pattern of amino acids entering the central nervous system.

The basic action of lactulose in HE is aimed at reducing 'nitrogenous intoxication' by decreasing blood ammonia concentration. Lactulose is degraded in the large bowel bacterial flora, mainly to acetic and lactic acids, thus reducing the intraluminal pH to below pH 5.0. This acidification of colonic contents results in the retention of ammonia as the ammonium ion $(NH4)^{+}$. In effect ammonia, amines and various amides, and other basic nitrogenous substances are thus trapped reducing their absorption into the blood. Since the colonic contents are more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the ammonium ion. Lowering of faecal pH is also thought to suppress urease-producing organisms, and to foster the growth of saccharolytic bacterial (*Lactobacillus acidophilus*) rather than *E.Coli* a more efficient ammonia producing bacterium. The diarrhoeal action of lactulose is synergistic in repelling the trapped ammonium ion from the colon.

Thus, of several proposals, the therapeutic action of lactulose in ameliorating the symptoms of HE is considered to be the result of the following:

- Reduction of faecal pH leading to reduced ammonia absorption via non-ionic diffusion and/or diffusion of ammonia from the blood into the gut. The trapped ammonia is then excreted in the stools.
- Suppression of urease-producing organisms.
- Induction of an osmotic type of diarrhoea which diminishes faecal stasis with reduction of nitrogenous substances for ammonia production. Decreased absorption of ammonia from the gut also results from shortening intestinal transit time.

The actual mechanism may be a combination of these effects.

INDICATIONS

i) For the treatment of acute Hepatic Encephalopathy, and the prevention and treatment of chronic Hepatic Encephalopathy, including the stages of hepatic pre-coma and coma.

ii) For the treatment of chronic and habitual constipation.

iii) Where a soft stool is considered of medical benefit (haemorrhoids, post colonic/anal surgery).

CONTRAINDICATIONS

Contraindicated in patients with

- Hypersensitivity to the active substance or to any of the excipients
- Galactosaemia
- Gastrointestinal obstruction, digestive perforation, or risk of digestive perforation

PRECAUTIONS

Consultation of a physician is advised in case of:

- Painful abdominal symptoms of undetermined cause before the treatment is started
- Insufficient therapeutic effects after several days.

A theoretical hazard may exist for patients treated with lactulose who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. If sugars reach the colon then bacterial breakdown causes hydrogen production. Accumulation of hydrogen gas in significant concentration in the presence of an electrical spark may result in an explosive reaction. Although this complication has not been reported with lactulose, patients on lactulose therapy undergoing such procedures should have a thorough bowel cleansing with non-fermentable solution.

Duphalac contains galactose (1.5 g or less per 15 mL) and lactose (0.9 g or less per 15 mL) and should be used with caution in diabetics as blood glucose levels may be elevated, usually after extended use.

Patients with rare hereditary problems of galactose or fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Lactulose should be administered with care to patients who are intolerant to lactose.

Chronic misuse of laxatives may result in electrolyte imbalance in particular serum potassium levels may be decreased. Elderly debilitated patients who receive Duphalac for more than six months should have serum electrolytes measured periodically.

When administered as a retention enema, due to strong cathartic effect, faecal incontinence, bedsoiling, and peri-anal irritation due to the acidic stool can be expected. The hydration status of the patient should be observed carefully.

In the overall management of Hepatic Encephalopathy, it should be recognised that there is a pre-existing liver disease and efforts should be made to identify and treat the precipitating cause of hepatic coma. Thus the overall management of hepatic encephalopathy should include dietary protein restriction bowel cleansing and sterilisation, correction of electrolyte and fluid imbalance, provision of caloric and nutritional needs and treatment of underlying liver disease.

Use in Pregnancy

Lactulose has been shown to be effective for the treatment of constipation associated with pregnancy when administered to women at different stages of pregnancy.

Reproduction studies with daily oral doses of lactulose (50% w/w) up to 12 mL per kg in mice and rats and 6 mL per kg in rabbits have not revealed any evidence of an increased occurrence of foetal damage or other deleterious effects.

Use in Lactation

There are no data on the secretion of lactulose in breast milk or the effect on the breast-fed infant. Risk-benefit should be considered.

Paediatric Use

It is recommended that if Duphalac is given to infants and children this should be done under medical supervision. The defaecation reflex may be altered during the treatment with lactulose (see Clinical Pharmacology). This alteration is considered to improve bowel habits during constipation and can be seen as a normalization of stool frequency.

Effects on ability to drive and use machines

Lactulose has no or negligible influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

There have been conflicting reports about the concomitant use of neomycin and lactulose although in some situations the two drugs administered together are more effective than either one alone.

Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. There have been some reports that lactulose-fermenting bacteria are relatively resistant to neomycin, which might explain why a combination could work in some cases. Thus the status of the lactulose-treated patient should be closely monitored (including stool pH) in the event of concomitant oral antibiotic therapy.

ADVERSE EFFECTS

Initial dosing may produce gaseous distension with flatulence and intestinal cramps in about 20% of patients. These effects are usually mild and transient.

Excessive dosage can lead to diarrhoea. If untreated potential complications of diarrhoea may include fluid loss, and electrolyte disturbances such as hypokalaemia and hypernatraemia.

Less frequently, nausea, vomiting, anorexia and increased thirst have been reported.

The following undesirable effects have been experienced with the below indicated frequencies in lactulose-treated patients in placebo-controlled clinical trials [very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data)].

	Frequency Category				
	Very Common	Common	Uncommon	Rare	Unknown
Gastrointestinal Disorders	Diarrhoea	Flatulence, abdominal pain, nausea, vomiting			
Metabolism and Nutrition					Anorexia

Disorders					
Investigations			Electrolyte imbalance due to diarrhoea		
General Disorders and Administration Site Conditions					Increased thirst

Paediatric Population:

The safety profile in children is expected to be similar as in adults.

DOSAGE AND ADMINISTRATION

The lactulose solution may be administered diluted or undiluted. The dose should be titrated according to the clinical response. A single dose of lactulose should be swallowed in one and should not be kept in the mouth for an extended period of time.

Hepatic Encephalopathy The safety and efficacy of lactulose use in children (newborn to 18 years of age) with HE have not been established. No data are available.

Dosing in HE (for adults only): The usual dosage is 30 to 45 mL three to four times daily. The dosage may be adjusted every day or two to produce two or three soft stools daily.

Hourly doses of 30 to 45 mL of Duphalac may be used to induce the rapid laxation indicated in the initial phase of the therapy of Hepatic Encephalopathy. When the laxative effect has been achieved, the dose of Duphalac may then be reduced to the usual daily dosage.

Improvement in the patient's condition may take 24-48 hours to occur. Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of Hepatic Encephalopathy. The dose of Duphalac for this purpose is the same as the usual daily dose.

In the treatment of acute episodes of Hepatic Encephalopathy a rapid response is desirable. In such cases it is important to avoid underdosage, and 50 mL every 1-2 hours can be given if necessary, until two loose bowel actions have occurred. Thereafter doses may be reduced to usual doses (30 to 45 mL three to four times daily).

The administration of Duphalac as a retention enema is an alternative technique. This can be done by diluting Duphalac and is of considerable value especially in the unconscious patient. In such cases 300 mL of Duphalac may be mixed with 700 mL of water or normal saline to be used as a retention enema; the enema is to be retained for 30-60 minutes, and repeated every 4-6 hours until the patient is able to take oral medication.

Chronic Constipation

Lactulose may be given as a single daily dose or in two divided doses, using the measuring cup.

All dosages should be adjusted to the needs of the individual. In case of single daily dose, this should be taken at the same time, e.g. during breakfast.

More serious constipation, and/or constipation such as caused by chemotherapy agents may require higher dosages.

	Duphalac oral solution	
	Starting dose (3 days)	Maintenance dose
Adults	15 - 45 mL	15 - 30 mL
Children (7 – 14 years)	15 mL	10 - 15 mL
Children (1 – 6 years)	5 - 10 mL	5 - 10 mL
Infants under 1 year	up to 5 mL	up to 5 mL

When experiencing constipation patients should be advised to drink plenty of water, and increase the fibre content in their diet.

OVERDOSAGE

No toxicity in humans has been recorded to date. There have been no reports of accidental overdosage. In the event of acute overdosage it is expected that diarrhoea and abdominal cramps would be the main symptoms. Complications of diarrhoea may include fluid loss, and electrolyte disturbances, such as hypokalaemia and hypernatraemia, in which case treatment would consist of fluid and electrolyte replacement. Treatment would include cessation of lactulose or dose reduction.

PRESENTATION AND STORAGE CONDITIONS

Bottle containing 200 mL or 500 mL

NAME AND ADDRESS OF THE SPONSOR

BGP Products Pty Ltd
299 Lane Cove Road
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF FIRST INCLUSION IN THE ARTG

ARTG Start date: 28 August 1991

DATE OF MOST RECENT AMENDMENT

06 October 2016